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EFFECTS OF THEOPHYLLINE INGESTION ON THERMOREGULATION DURING 15°C WATER IMMERSION

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TABLE OF CONTENTS

EXECUTIVE SUMMARY

Military personnel can be exposed to emergency survival conditions in cold environments which could result in lethal levels of hypothermia if appropriate insulation or protective shelters are not available. Hypothermia can be delayed in humans if metabolic heat production is increased, and we have previously demonstrated that pre-treatment with certain safe pharmacological agents can elicit such an effect. Others have reported that the ingestion of theophylline, a caffeine-like compound, delays the onset of hypothermia during acute cold air exposure. The present study was carried out to determine if theophylline treatment will delay the onset of hypothermia during a more severe cold stress, i.e. cold water immersion. Eight male subjects were immersed in 15°C water on several different days after treatment with placebo, theophylline, or either of these combined with a standard meal. Although there were indications that the theophylline treatment, particularly when combined with the meal, increased metabolic heat production prior to immersion, there were no significant differences between trials in metabolic heat production during the water immersion. Rectal temperature decreased similarly in all trials at a rate ranging between 0.4 to 3.0°C/h. Thus, the beneficial effects of theophylline treatment that were previously reported for cold air exposure may not be applicable to cold water immersion.

ABSTRACT

Studies in rats and humans have demonstrated that substrate feeding (Ensure®, 1480 kJ/235 ml) and/or treatment with theophylline (TH) results in a slower rectal temperature (T_{re}) decrease during cold air exposure. The implication is that ingestion of this drug may significantly delay the time to onset of hypothermia during acute cold exposure. The present study investigated the effects of TH and 1480 kJ of mixed substrate feeding (EN) on thermoregulation in humans during immersion in 15°C water. The experiment was a double-blind repeated measures design, where each of the 8 male subjects was immersed (head out of water) in a whole body water calorimeter after each of the following treatments: TH, placebo (PL), TH + EN, and PL + EN. T_{re} and metabolic rates were recorded before and during the immersion; heat loss to the calorimeter was measured during the immersion; and venous blood samples were taken before and during the immersion. Blood glucose and/or FFA levels were significantly elevated prior to immersion in TH, TH + EN, and PL + EN when compared with the PL trial. The pre-immersion rate of metabolic heat production was significantly increased by the TH+EN treatment. Immersion increased the metabolic rates to a mean of 3-4 times resting values and this increase was similar among trials. The rates of decrease in T_{re} ranged among the subjects from 0.4 to 3.0°C/h. These mean rates of decrease of T_{re} and the rate of heat loss measured by the calorimeter were similar for all treatments. Thus, the beneficial effects of TH + EN treatments that were previously reported for cold air exposure may not be applicable to cold water immersion.

INTRODUCTION

It was reported that theophylline ingestion by human subjects, combined with substrate feeding, was associated with a significantly slower rate of decrease in rectal temperature (T_{re}) during three hours of intermittent rest and light exercise in cold air ranging from -5 to 15°C (14). The mechanism of action was initially attributed to either an inhibition by theophylline of cAMP phosphodiesterase, and/or adenosine receptor antagonistic effects. Phosphodiesterase inhibition would increase cAMP concentration and act via "second messenger" effects to stimulate substrate mobilization and utilization, while adenosine receptor antagonism is purported to reduce the inhibition of lipolysis associated with adenosine (14). More recent studies support a relatively more important role of adenosine receptor antagonism (13). It is noteworthy that "cold resistance" did not improve after theophylline treatment alone in subjects who simply rested in cold air (15). In these same subjects there was, however, a beneficial effect of feeding alone, which was equal to that caused by the combination of feeding and theophylline treatments. Thus, Wang et al. (14) concluded that the differences between the results of experiments done on resting and intermittently exercising subjects suggest that metabolic rate must be higher than that caused by cold air exposure alone in order to exploit the potential for increased heat production associated with theophylline ingestion.

The practical significance of these findings is the implication that ingestion of this drug may significantly delay the time to onset of hypothermia during acute cold exposure. Since cold water immersion of unclothed subjects stimulates a much more rapid and extensive increase in metabolic rate than does cold air exposure, we speculated that subjects resting and shivering in water may also exhibit a delayed decrease in T_{re} after theophylline treatment. Therefore, the present investigation was designed to test the hypothesis that theophylline treatment prior to cold water immersion would delay the rate of decrease of T_{re}. Since previous research suggests that theophylline's effects are optimized if some food is ingested together with the drug (12), the effects of the drug were evaluated in conjunction with a standardized feeding.

MATERIALS AND METHODS

After review and approval of the experimental protocol by the institutional ethics committee, eight healthy, male subjects volunteered to participate. They were 21-35 y old and were relatively lean with the percentage of body weight consisting of fat ranging from 10-17%. All risks and discomforts associated with the protocol were explained and written informed consent was obtained.

Protocol

The subjects visited the laboratory on five test days. During the first test day they were medically screened for contraindications to their participation.

Hydrostatic weighing techniques were used to estimate body density and calculate body fat content (1). They then underwent a short familiarization immersion for 20 min to become accustomed to the cold water, and the various methods and equipment used for physiological monitoring during the immersions.

The subsequent four trials were done at weekly intervals at the same time of day. Treatments were administered in a double-blind fashion with regard to the theophylline or placebo administration, and an attempt was made to balance the order of trials among the subjects; the treatments prior to immersion were placebo (PL), theophylline (TH), PL and feeding (PL+EN), and TH and feeding (TH+EN). TH was ingested as the sustained release theophylline compound oxtriphylline (Choledyl SA®), the theophylline salt of choline containing 64% theophylline. Two 400 mg tablets were ingested per day (one tablet in the morning and evening) over 2.5 days prior to the day of the immersion. The instructions for the PL ingestion were the same; PL was two 250 mg tablets of calcium carbonate. The feeding treatments were in the form of a standard meal consumed 45 min before the immersion. The meal was a commercially available nutritional supplement (Ensure Plus ®) which consisted of 235 mL of liquid containing 1480 kJ (355 kcal). The nutritional composition per 100 mL was: 5.75 g protein, 5.36 g fat, 19.91 g carbohydrate, 76.79 g water, plus vitamins and electrolytes.

Blood Sampling

Prior to all water immersions, a Teflon catheter (Deseret, Sandy, UT) was inserted into an antecubital vein and kept patent by a slow infusion (1 $mL \cdot min^{-1}$) of isotonic saline containing no heparin. The subjects reclined for 30 min at the end of which resting metabolic rate was determined during a 10 min period. Blood samples were then drawn and taken again at 5, 20, 40, 60 min of immersion and/or just prior to removing the subject from the water. During the immersion the arm with the catheter was not entirely immersed, but lay on a piece of Styrofoam floating on the water surface. The blood was treated and subsequently assayed for the serum levels of theophylline (Baxter Labs ^{125}I Theophylline Radioimmunoassay Kit), thyroxine (2) and triiodothyronine (3) and the plasma concentrations of free fatty acids (Wako Pure Chemical nonesterified fatty acids assay), glucose and lactate (10), glucagon (Cambridge Medical Diagnostics ^{125}I Glucagon Radioimmunoassay Kit), insulin (Serono Laboratories Radioimmunoassay Kit polyethylene glycol method), epinephrine and norepinephrine (Upjohn Diagnostics Cat-A-Kit® radioenzymatic assay kit [^{3}H]).

Calorimetry and Temperature Measurements

All water immersions took place in a whole body water calorimeter situated in a temperature control room maintained at 21°C. A detailed description of the calorimeter can be found elsewhere (4, 6). Briefly, the subject was placed supine in a horizontal immersion cage with only head and upper neck protruding. The cage was connected to an electric winch and was quickly lowered into the calorimeter. The water temperature in the calorimeter was maintained at 15.0±0.1°C by a control

system which detects a rise in the water bath temperature and, in response, permits water at 5°C to pass through a heat exchanger in the bath. By measuring the volume of cold water collected from the heat exchanger that was required to equilibrate and maintain the water bath temperature, total heat loss from the body can be calculated. The mean rate of heat loss from the body to the calorimeter was calculated by dividing the measured heat gained by the calorimeter by the immersion time.

The subjects were immersed to the level of the clavicle. Immersions were terminated when any of the following occurred. T_{re} reached 35.5°C or decreased by 1°C, or when 90 min had elapsed. Using these criteria, the immersion time varied within and between subjects; thus for purposes of comparing a maximum number of subjects with a repeated measures design, data for several variables are shown for up to 40 min of immersion.

During the water immersion T_{re} was monitored from a thermistor (model 400, Yellow Springs Instruments, Yellow Springs, OH) inserted 16 cm beyond the anal sphincter. The rate of fall of T_{re} was calculated as the net change of T_{re} divided by the total immersion time. Oxygen uptake ($\dot{V}O_2$) and respiratory exchange ratio (RER), calculated from $\dot{V}O_2$ and carbon dioxide production, were monitored during the immersion using open-circuit spirometry with an automated system (Alpha Technologies System 4400). The minute-by-minute values were averaged over five minute intervals, and these average values were subsequently used for statistical comparisons and for calculations of metabolic rates. The rate of metabolic heat production from fat and carbohydrate oxidation was calculated from the mean $\dot{V}O_2$ values and the energy yield per litre of consumed oxygen corresponding to the RER values (8). Protein oxidation is negligible during cold exposure (11), thus the measured RER was assumed to be equal to the nonprotein RER. The first five minutes of immersion were excluded from the calculations because of hyperventilation, which invalidates the use of RER for calculating metabolic rate. The subjects were rewarmed in a hot tub with the water temperature controlled at 39-40°C.

Statistics

The effects of the treatments on the pre-immersion data were analyzed with a one factor repeated measures analysis of variance (ANOVA) using micro-computer statistical software (SuperANOVA®, Accessible General Linear Modeling, Abacus Concepts, 1989). The variables measured before and during the water immersion were then analyzed with a two factor (treatment and time) ANOVA. When a significant ($p<0.05$) main effect of one of the factors or interaction of factors was indicated, then the trial means were contrasted to determine which means differed significantly. Data are expressed as means±SD.

RESULTS

Cooling Rate and Calorimetry

There were no significant differences between trials for the total immersion time; mean values were 65.0±25.3 min for PL, 69.1±31.2 min for PL+EN, 66.2±29.8 min for TH and 71.2±27.0 for TH+EN. The overall rate of change of T_{re} was similar across trials and averaged 1.1±0.9°C•h^{-1} during the entire immersion period. Because of the large inter-subject variation in immersion time, comparisons of variables measured during the immersion have been limited to 40 min of immersion. The effect of the treatments on T_{re} during 40 min is depicted in Figure 1; there were no signficant inter-trial differences.

Table 1 shows that there was a significant effect of the treatments on the pre-immersion RER, but not the $\dot{V}O_2$. The RER for PL and TH were similar; PL+EN was higher than PL, TH and TH+EN; TH+EN, however, was not different from TH. When the pre-immersion rate of metabolic heat production was calculated based on the RER and $\dot{V}O_2$ data, there was a significant effect of the treatments; this was due to PL+EN being significantly lower than both TH and TH+EN (Table 1).

The RER was significantly lower during immersion compared to pre-immersion values, and the $\dot{V}O_2$ and calculated rate of metabolic heat production increased progressively during the immersions; there were no differences among trials (Figure 2). Technical difficulties caused the loss of some data for two subjects during the immersions, thus their metabolic rate data were not included in the analysis shown in Figure 2; the pre-immersion data shown in Table 1, however, were available for all subjects explaining the difference between Table 1 and Figure 2 pre-immersion mean values.

We assume that the rate of body heat loss prior to immersion was approximately equivalent to heat production since T_{re} was stable. Compared to pre-immersion values there was a dramatic increase in the measured mean rate of heat loss to the calorimeter during the immersion by about seven-fold, but there were no differences between trials: 305±78, 299±87, 296±68, and 297±64 watts•m^{-2} body surface area for PL, PL+EN, TH, and TH+EN, respectively. It should be noted that these values are underestimations of the true whole body heat loss since the head and one arm were not immersed; although the heat losses from the head and arm and those due to respiration were not measured, we presume that they were proportional to the calorimetrically measured losses and, hence, relatively constant between trials.

Blood Metabolites And Hormones

Serum theophylline levels were undetectable for the two PL trials and were increased significantly to a mean value of 26±10 µmol•L^{-1} prior to immersion for

both TH trials, with no difference between TH and TH+EN. The effect of the treatments on the other variables measured just prior to the water immersion is shown in Table 2. The EN treatments both caused increases in pre-immersion glucose and insulin levels such that values for PL+EN were significantly greater than PL, and TH+EN was greater than TH. There were no significant inter-trial differences for the pre-immersion blood catecholamine, glucagon, thyroxine, or triiodothyronine concentrations. The pre-immersion free fatty acid levels tended to be higher for the TH trials compared to the placebo trials, but failed to achieve statistical significance ($p=0.07$).

As was discussed above, technical difficulties caused the loss of some data for two subjects during the immersions, thus their data were not included in the analyses shown in Figures 3-5; the pre-immersion data shown in Table 2, however, were available for all subjects explaining the difference between Table 2 and the pre-immersion mean values shown in Figures 3-5.

Similar to the pre-immersion effects, significant treatment effects on glucose and insulin were observed during the immersion. The EN trial insulin values were higher than their respective control trials, but not different from each other (Figure 3). There was also a significant main effect of the water immersion on glucose but it must be considered in light of the significant interaction of the time and treatment factors; the decrease in glucose of about 1 $mmol \cdot L^{-1}$ was due to the change during the two EN trials.

Water immersion significantly increased the epinephrine and norepinephrine values (Figure 4). There was also a treatment effect measured for the norepinephrine concentrations; TH was greater than TH+EN and both of these were greater than both PL trials.

There was a main effect of time, tempered by a significant time-by-trial interaction on the free fatty acid concentrations during the immersions. Compared to pre-immersion values there was a significant decrease only for both TH trials, attributable to their somewhat higher pre-immersion values (Figure 5).

Both T3 and T4 increased significantly during the immersion compared to the pre-immersion values but there was no treatment effect: when the value for all trials was combined T3 increased from 1.4±0.3 to 1.6±0.3 $ng \cdot mL^{-1}$, and T4 increased from 7.4±2.0 to 8.4±2.0 $\mu g \cdot dL^{-1}$.

DISCUSSION

The main objective of this investigation was to determine if the reduced rate of cooling during cold air exposure reported after theophylline treatment combined with substrate feeding (14) would also be observed during cold water immersion. Our main finding was that there were no significant treatment effects on the rate of metabolic heat production or the kinetics of rectal temperature during the water immersion.

The theophylline treatment we employed was identical to that reported by Wang et al. (14), and resulted in similar plasma theophylline concentrations. If the adenosine receptor antagonism caused by theophylline did reduce the inhibition of adenosine on lipolysis, then we expected to observe indications of a greater degree of lipid metabolism after TH treatments. This was confirmed indirectly by the pre-immersion RER measurements (Table 1). The EN feedings caused the expected increase in RER for the PL+EN trial, because the higher blood glucose should cause greater carbohydrate oxidation from a simple mass action effect, and the associated increases in insulin are anti-lipolytic. A similar effect was not observed, however, for TH+EN; this RER value was not different from the trials conducted without the substrate feeding, in spite of the fact that the glucose and insulin values were similar to PL+EN. Thus, the potential anti-lipolytic effects of the higher insulin and glucose levels in TH+EN were apparently blunted, and this interpretation is consistent with a greater rate of lipolysis. The FFA mean values for TH and TH+EN tended to be somewhat higher than the PL trials ($p=0.07$). Taken together, the RER and FFA values suggest that lipolysis and the rate of lipid oxidation were somewhat more accelerated as a result of TH treatments. This observation is consistent with the demonstration that theophylline-enhanced thermogenesis in rats is mediated by adenosine receptor antagonism (13, 7).

The calculated resting metabolic rate, thus heat production, prior to water immersion was about 20% greater after the theophylline combined with substrate feeding treatment. It is tempting to simply attribute the elevated metabolic rate to the thermic effect of consuming and digesting the ingested substrate. There was, however, no similar detectable increase when EN was ingested during the PL+EN trial.

Although we may interpret out data as suggesting that the subjects were indeed physiologically predisposed after the TH+EN treatment for a greater thermogenesis during the subsequent water immersion, such was not observed. These results contrast with those reported earlier for cold air exposure (14). There were several important differences between the studies in the manner in which the cold stress was induced. Wang et al. (14) exposed their subjects to cold air for 180 min and they adjusted the air temperature for each subject so that T_{re} would decrease by about 1°C during the three hours. The purpose of the individual temperature titration was to standardize the relative cold stress among subjects. The actual air temperature required to achieve this objective ranged from -5° to 15°C, but the same temperature was used during all trials for any given subject.

In the present study, all the subjects were immersed in 15°C water, thus the rate of heat loss was almost immediately over three times greater than metabolic rate, and resulted in a decrease in T_{re} that was observable on average after about 15 min of immersion, and in some subjects after only 5 min in the water. Contrast this with the cold air medium; during the first hour of the cold air trials by Wang et al. (14), metabolic rate was apparently able to match heat loss because there was no significant change in T_{re}. Their subjects alternated between intermittent exercise

for 10 min and 20 min of rest throughout the cold exposure, thus their calculated rate of metabolic heat production cycled between 3.4 times resting rates during the resting state to a mean value of over six times resting rates during the exercise. They reported no significant inter-trial differences in the detectable metabolic heat production. They did report, however, that the slope of the regression of T_{re} against time was significantly less for their TH+EN trial than for their PL trial. As a result, T_{re} was higher at the end of their TH+EN trial than the PL trials, but not different from the TH trial. This could have been due to an increased thermogenesis, the extent of which was below the sensitivity of the equipment used to monitor their metabolic rates, or a decreased rate of heat loss. It was reported that skin temperature was similar for all trials, thus the latter explanation is probably not relevant.

The cold-induced increases in epinephrine, norepinephrine, T3 and T4 are consistent with our earlier observations (5, 9). Any changes in blood metabolite or hormone concentrations associated with cold water immersion should be interpreted carefully, however, because there is a substantial decrease in plasma volume, which can amount to over 20% (9). TH treatment was reported by Wang et al. (14) to be associated with greater relative changes in norepinephrine than the PL trials. Their pre-cold exposure norepinephrine concentrations were, however, unusually high. The mean value was 2417 $pg \cdot mL^{-1}$, over 10 times normal values. Their initial epinephrine values were also high, and these high catecholamine concentrations can probably be attributed to nervousness associated with the blood sampling procedure since the samples were drawn immediately after insertion of the catheter. We also observed, though, significantly higher norepinephrine levels during the immersions after TH and TH+EN treatments. An α-adrenergic receptor mediated increase in vasoconstriction might be expected to reduce heat loss because of these higher norepinephrine levels, but our measurements of heat loss to the water calorimeter do not support such an explanation.

In conclusion, the present study demonstrated that theophylline pre-treatment alone did not affect the rate of decrease of rectal temperature, contrasting with earlier rat studies and studies on humans exposed to cold air. When comparing the rates of heat loss in these two media, i.e. cold air vs. cold water, with hindsight, perhaps it was unreasonable to expect that the slight difference in the time course of change of T_{re} attributed to theophylline during cold air could offset the rapid and large rates of heat loss that occur in cold water. We suggest that any potential for increased metabolic heat production caused by the theophylline treatment alone is not likely to delay hypothermia in cold water.

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	PL	PL+EN	TH	TH+EN
Oxygen consumption ($L \cdot min^{-1}$)	0.302±0.054	0.289±0.069	0.331±0.052	0.344±0.052
RER	0.838±0.064*	0.934±0.055	0.822±0.063*	0.862±0.051*
Metabolic heat (watts•m^{-2} BSA)	42.3±7.2	39.9±10.6	47.7±4.3†	48.4±9.0†

* significantly different from PL+EN
† significantly different from PL+ EN

Table 1. Pre-immersion gas exchange and calculated metabolic rate variables after treatments with placebo (PL), PL and feeding (PL+EN), theophylline (TH) and TH and feeding (TH+EN). Data are mean values ± SD.

	PL	PL+EN	TH	TH+EN
Free fatty acids ($mmol \cdot L^{-1}$)	0.792±0.226	0.572±0.271	0.978±0.438	0.868±0.395
Glucose ($mmol \cdot L^{-1}$)	4.4±0.6	5.2±1.0 *	4.7±0.7	5.8±0.9 †
Insulin ($\mu U \cdot mL^{-1}$)	5.4±2.2	37.2±9.8 *	7.9±3.6	42.2±10.1 †
Glucagon ($pg \cdot mL^{-1}$)	412±195	429±257	466±256	421±239
Epinephrine ($pg \cdot mL^{-1}$)	46±35	49±32	60±37	44±34
Norepinephrine ($pg \cdot mL^{-1}$)	276±171	335±210	314±169	361±209
Thyroxine ($\mu g \cdot dL^{-1}$)	7.3±1.3	7.4±1.2	8.0±1.9	7.5±1.5
Triiodothyronine ($ng \cdot mL^{-1}$)	1.2±0.3	1.4±0.2	1.4±0.4	1.5±0.2

* significantly different from PL
† significantly different from TH

Table 2. Pre-immersion blood concentrations after treatments with placebo (PL), PL and feeding (PL+EN), theophylline (TH) and TH and feeding (TH+EN). Data are mean values ± SD.

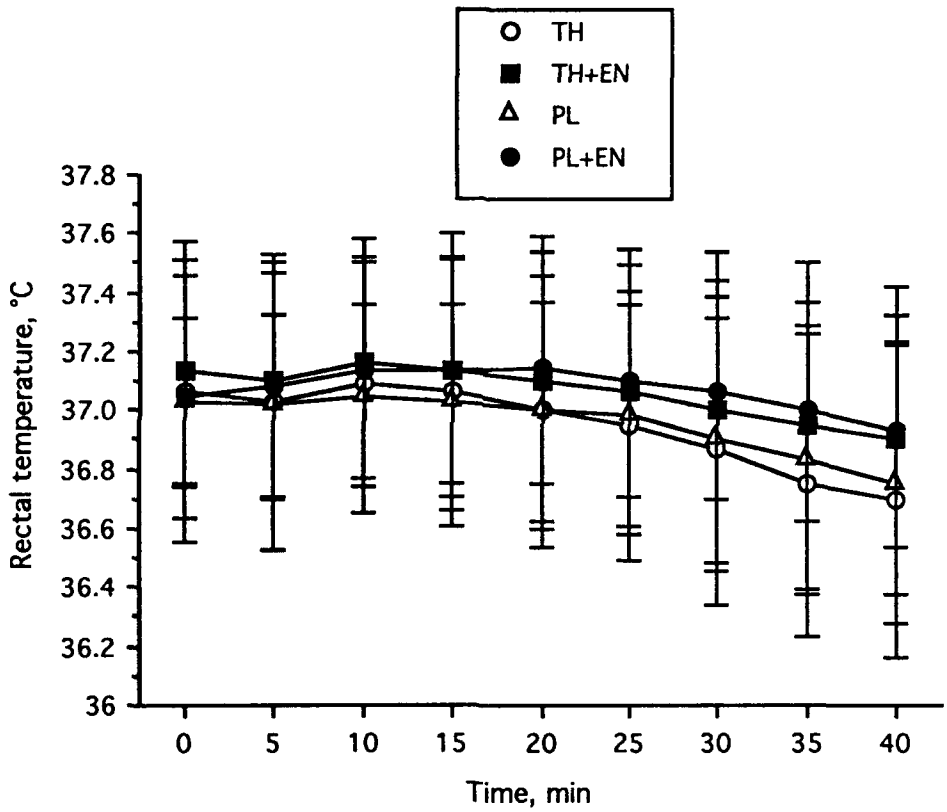

Figure 1. Mean changes in rectal temperature during immersion in 15°C water after treatment with placebo (PL) theophylline (TH), PL and a mixed substrate feeding containing 1480 kJ (PL+EN), and TH+EN. Data are shown as mean values and standard deviation.

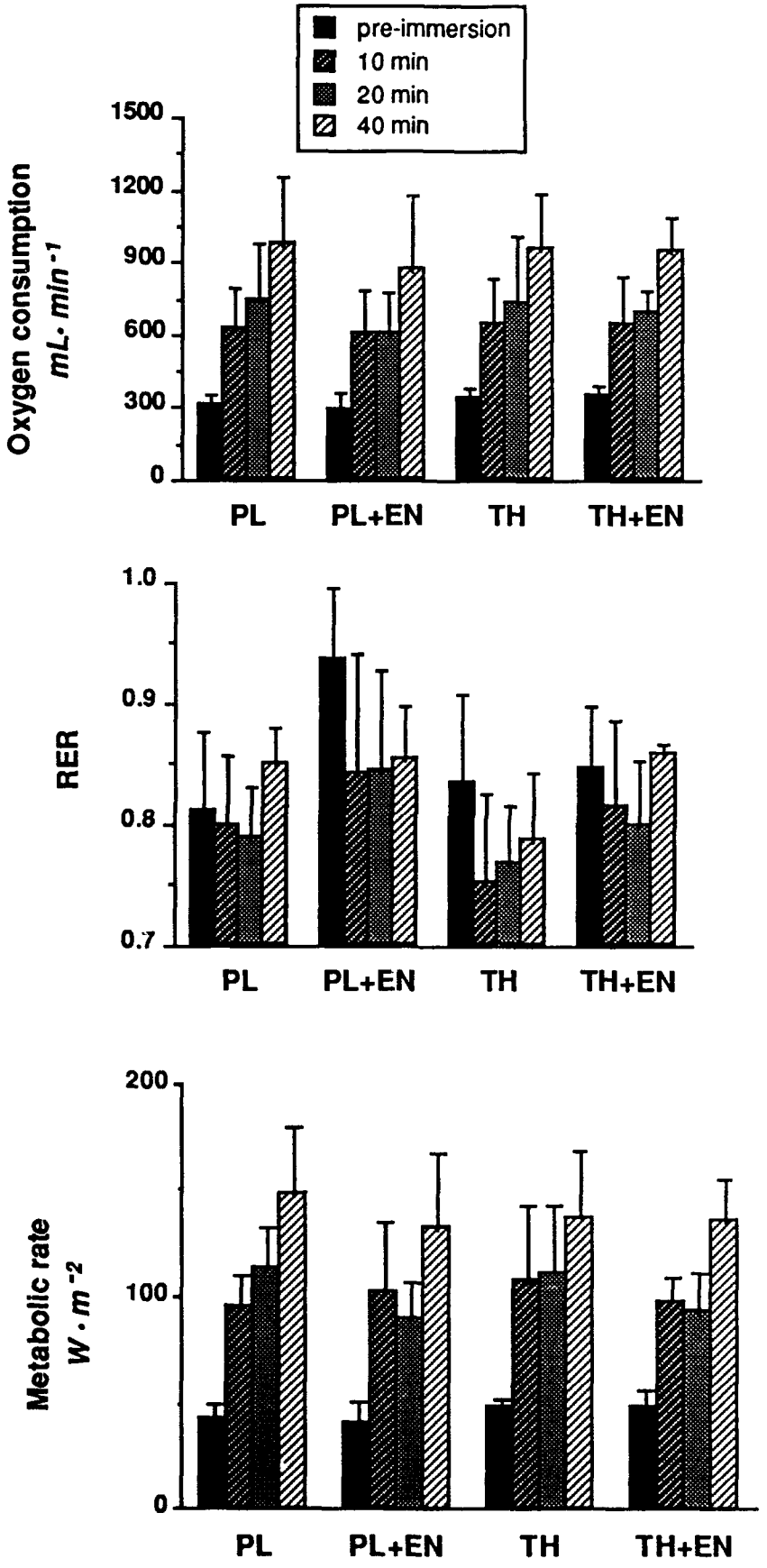

Figure 2. Changes in oxygen consumption, the respiratory exchange ratio, and the calculated metabolic rate. Data are shown as mean values and standard deviation. Abbreviations as in Fig. 1.

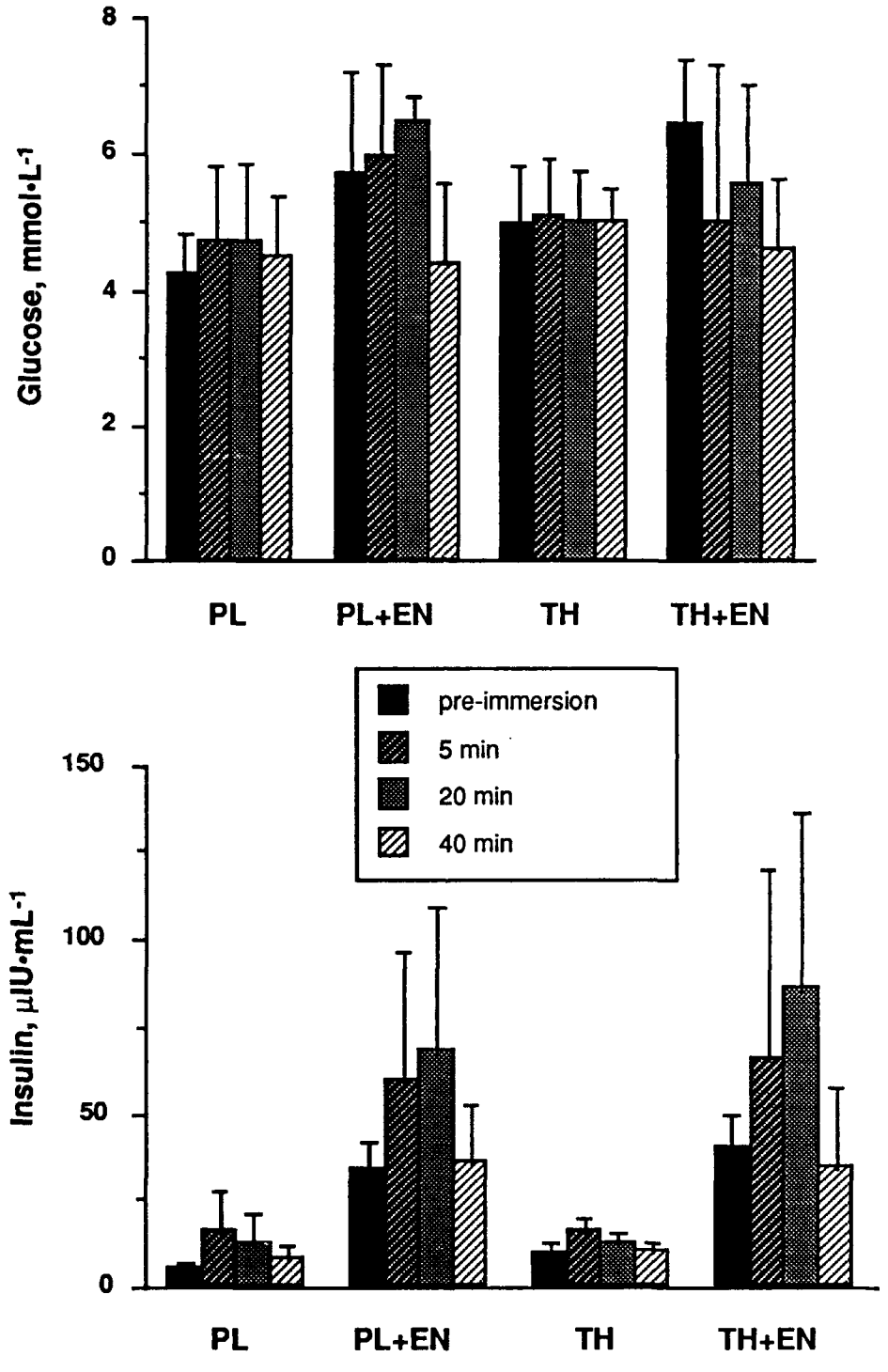

Figure 3. Changes in glucose and insulin concentrations. Data are shown as mean values and standard deviation. Abbreviations as in Fig. 1.

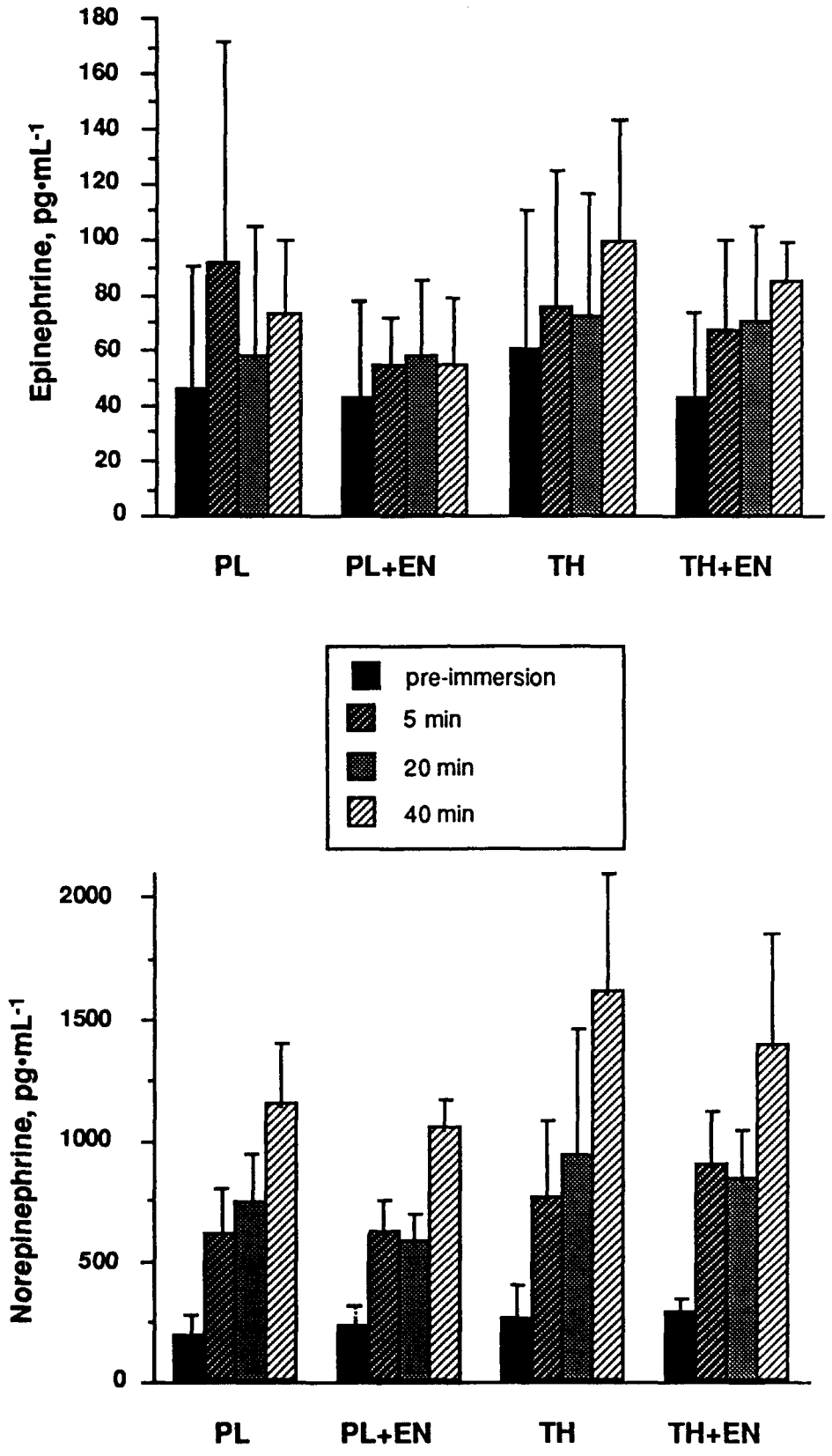

Figure 4. Changes in blood catecholamine concentrations. Data are shown as mean values and standard deviation. Abbreviations as in Fig. 1.

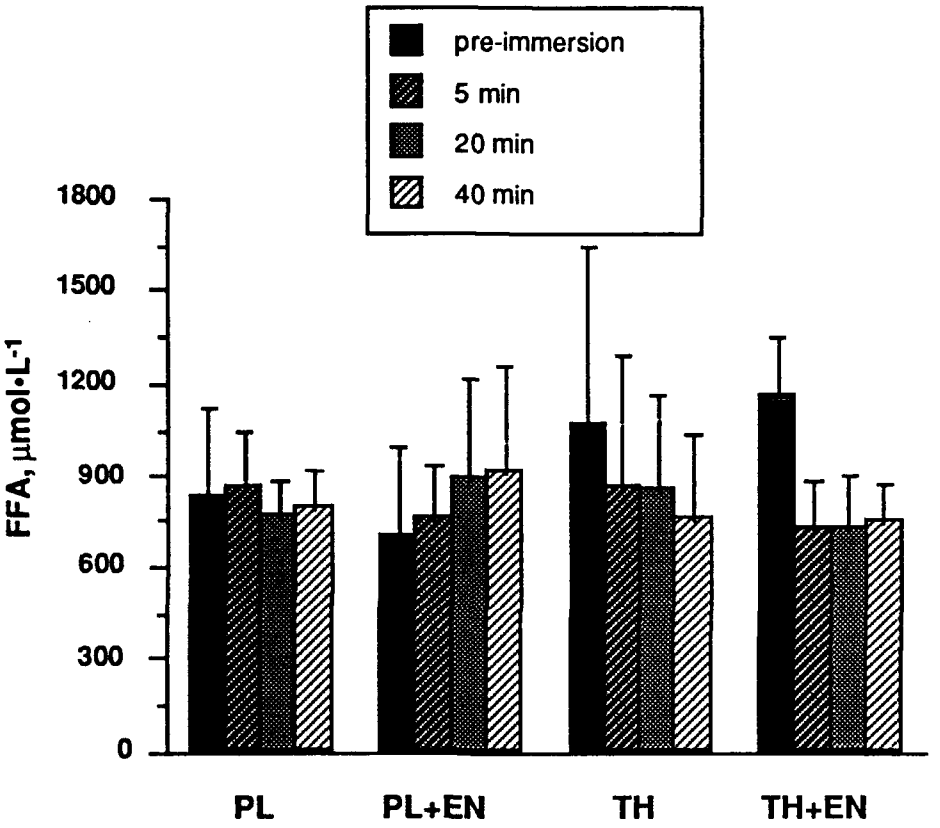

Figure 5. Changes in blood free fattyi acids (FFA) concentrations. Data are shown as mean values and standard deviation. Abbreviations as in Fig. 1.

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Military personnel can be exposed to emergency survival conditions in cold environments which could result in lethal levels of hypothermia if appropriate insulation or protective shelters are not available. Hypothermia can be delayed in humans if metabolic heat production is increased, and we have previously demonstrated that pre-treatment with certain safe pharmacological agents can elicit such an effect. Others have reported that the ingestion of theophylline, a caffeine-like compound, delays the onset of hypothermia during acute cold air exposure. The present study was carried out to determine if theophylline treatment will delay the onset of hypothermia during a more severe cold stress, i.e. cold water immersion. Eight male subjects were immersed in 15 deg C water on several different days after treatment with placebo, theophylline, or either of these combined with a standard meal. Although there were indications that the theophylline treatment, particularly when combined with the meal, increased metabolic heat production prior to immersion, there were no significant differences between trials in metabolic heat production during the water immersion. Rectal temperature decreased similarly in all trials at a rate ranging between 0.4 to 3.0 deg C/h. Thus, the beneficial effects of theophylline treatment that were previously reported for cold air exposure may not be applicable to cold water immersion.

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Hypothermia, metabolism, shivering, methyl-xanthine